Incidence and Risk Factors of Severe and Fatal Arrhythmia in FLT3-ITD Positive Acute Myeloid Leukemia Patients Treated with Quizartinib: Preliminary Results

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BACKGROUND

Quizartinib, an oral FLT3 inhibitor, was approved in the United States (US) in 2023, for the treatment of newly diagnosed FLT3-ITD positive acute myeloid leukemia (AML).

A post-marketing study was required by the US Food and Drug Administration to evaluate the incidence and risk factors of severe ventricular arrhythmia (VA) and sudden cardiac arrest (SCA) among quizartinib-treated AML patients.

CONCLUSION

In the first year of this study, the cumulative incidence of severe or fatal VA/SCA was 2.8% for quizartinib (95% CI: 0.3–9.8%), 2.3% for standard 7+3 chemotherapy (95% CI: 1.1–4.4%), 3.2% for midostaurin (95% CI: 1.1–7.4%), and 4.8% for gilteritinib (95% CI: 2.8–7.8%). In this preliminary analysis, there were numerical differences in patient and clinical characteristics, and potential risk factors for VA/SCA.

Only 2 out of 71 quizartinib-treated patients developed a severe arrhythmia event, and neither was fatal. Both events occurred within one month of initiating quizartinib, with both patients using concomitant medications with a known, possible, or conditional risk of TdP at the time of the event. The analyses in future years of this study may benefit from sample size and potential outcome accrual to improve incidence estimate precision, and unstructured data access to conduct validation, obtain additional clinical features of outcome events, and enhance the risk factor assessment.

OBJECTIVES

To describe first-year findings from a multi-year post-marketing safety study evaluating: (i) the incidence of severe and fatal VA/SCA among quizartinib-treated AML patients, (ii) clinical features and temporal patterns of VA/SCA events, and (iii) associations between VA/SCA and potential risk factors. An exploratory objective was to contextualize VA/SCA incidence in quizartinib-treated patients relative to other FLT3 inhibitors and to standard 7+3 chemotherapy.

METHODS

This observational cohort study used the TriNetX Dataworks-USA network, comprising de-identified EHR data from >110 million patients across 72 U.S. healthcare organizations. Adult AML patients initiating quizartinib between August 1, 2023 and June 5, 2025, with ≥12 months of prior EHR activity were included.

The primary outcome was a composite of severe (grade 3-4) and fatal (grade 5) VA/SCA identified using a previously validated algorithm supplemented with diagnosis codes selected by subject-matter experts. Cumulative incidence and incidence rates with 95% confidence intervals (CI) were estimated. Baseline demographics, AML characteristics, arrhythmia-related comorbidities, electrolyte abnormalities, and concomitant medications associated with Torsades de Pointes (TdP) risk were descriptively evaluated.

RESULTS

There were 112 patients who initiated quizartinib between 01 August 2023, and 05 June 2025. Of these, 71 patients had ≥1 interaction with the EHR network at least 12 months prior to the index date, resulting in 71 patients in the final quizartinib cohort. Additionally, there were 386 patients in the final standard 7+3 chemotherapy (without an FLT3 inhibitor) group, 154 patients in the final midostaurin group, and 330 patients in the final gilteritinib group who fulfilled selection criteria.

Quizartinib-treated patients had a mean age of 55.1 years (SD 13.1) and were predominantly female (54.9%) and White (78.9%). Standard 7+3 chemotherapy-treated patients had a mean age of 50.2 years (SD 19.6), were predominantly male (52.6%) and White (66.6%). Midostaurin-treated patients had a mean age of 51.9 years (SD 15.4), were predominantly female (54.5%) and White (66.9%). Gilteritinib-treated patients had a mean age of 60.6 years (SD 17.7), were evenly represented by sex (50.0% female, 49.1% male, 0.9% unknown), and were predominantly White (68.8%).

Table 1. Baseline demographic characteristics of quizartinib, standard 7+3 chemotherapy, midostaurin, and gilteritinib-treated patients.

Characteristic n (%)*	Quizartinib (n = 71)	Standard 7+3 Chemotherapy (n = 386)	Midostaurin (n = 154)	Gilteritinib (n = 330)
Age at index (years)				
Mean (SD)	55.1 (13.1)	50.2 (19.6)	51.9 (15.4)	60.6 (17.7)
Sex				
Female	39 (54.9)	175 (45.3)	84 (54.5)	165 (50.0)
Race				
White	56 (78.9)	257 (66.6)	103 (66.9)	227 (68.8)
Asian	5 (7.0)	25 (6.5)	9 (5.8)	24 (7.3)
Black or African American	4 (5.6)	45 (11.7)	21 (13.6)	44 (13.3)
Ethnicity				
Not Hispanic or Latino	53 (74.6)	308 (79.8)	112 (72.7)	255 (77.3)

Table 3. Baseline clinical characteristics of quizartinib, standard 7+3 chemotherapy, midostaurin, and gilteritinib-treated patients.

Characteristic n (%)	Quizartinib (n = 71)	Standard 7+3 Chemotherapy (n = 386)	Midostaurin (n = 154)	Gilteritinib (n = 330)
AML setting at index date				
Newly diagnosed	38 (53.5)	303 (78.5)	131 (85.1)	131 (39.7)
Relapsed/Refractory	33 (46.5)	83 (21.5)	23 (14.9)	199 (60.3)
Time since first AML record (time, in months, between first AML diagnosis and index date)				
Total (%)	69 (97.2)	386 (100.0)	154 (100.0)	330 (100.0)
Median (IQR)	0.8 (0.4, 15.2)	0.2 (0.1, 0.7)	0.5 (0.3, 1.1)	4.6 (1.3, 11.3)
FLT3 inhibitor use in the past 12 months	23 (32.4)	2 (0.5)	5 (3.2)	81 (24.5)
Duration of index treatment (days)				
Median (IQR)	38.0 (12.0, 93.0)	-	91.0 (34.0, 122.0)	102.5 (68.0, 211.0)
Concomitant Medication Use‡				
Use of medication with known risk of TdP	59 (83.1)	296 (76.7)	132 (85.7)	262 (79.4)
Use of medication with conditional risk of TdP	62 (87.3)	296 (76.7)	130 (84.4)	269 (81.5)
Use of antiarrhythmic medication	49 (69.0)	310 (80.3)	111 (72.1)	215 (65.2)

Table 2. Cumulative incidence and incidence rate of the primary outcome, severe and fatal VA/SCA, for quizartinib, standard 7+3 chemotherapy, midostaurin, and gilteritinib.

		Cumulative Incidence		Incidence Rate	
Primary Outcome	Number of Events	Number of Patients	Cumulative Incidence (95%CI)	Person Time (in years)	Rate per 1,000 Person-Years (95% CI)
Quizartinib	2	71	0.028 (0.003, 0.098)	12.2	163.642 (19.818, 591.133)
Standard 7+3 chemotherapy	9	386	0.023 (0.011, 0.044)	53.8	167.426 (76.558, 317.827)
Midostaurin	5	154	0.032 (0.011, 0.074)	39.4	126.876 (41.196, 296.086)
Gilteritinib	16	330	0.048 (0.028, 0.078)	139.0	115.107 (65.794, 186.927)

Table 4. Baseline laboratory and clinical values of quizartinib, standard 7+3 chemotherapy, midostaurin, and gilteritinib-treated patients.

Characteristic n (%)*	Quizartinib (n = 71)	Standard 7+3 Chemotherapy (n = 386)	Midostaurin (n = 154)	Gilteritinib (n = 330)
NCI Comorbidity Index Score				
0	30 (42.3)	165 (42.7)	73 (47.4)	140 (42.4)
>0 – <1	31 (43.7)	157 (40.7)	54 (35.1)	123 (37.3)
1 – <2	10 (14.1)	60 (15.5)	23 (14.9)	57 (17.3)
2 – <3	0 (0.0)	3 (0.8)	4 (2.6)	9 (2.7)
3 – <4	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
≥4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serum potassium				
Hyperkalemia	0 (0.0)	4 (1.0)	0 (0.0)	2 (0.6)
Normal	37 (52.1)	282 (73.1)	99 (64.3)	191 (57.9)
Hypokalemia	19 (26.8)	69 (17.9)	28 (18.2)	44 (13.3)
Severe hypokalemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	15 (21.1)	31 (8.0)	27 (17.5)	93 (28.2)
Serum magnesium				
Hypermagnesemia	1 (1.4)	13 (3.4)	7 (4.5)	3 (0.9)
Normal	40 (56.3)	235 (60.9)	81 (52.6)	129 (39.1)
Hypomagnesemia	6 (8.5)	17 (4.4)	7 (4.5)	22 (6.7)
Severe Hypomagnesemia	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	23 (32.4)	121 (31.3)	59 (38.3)	176 (53.3)
Serum calcium				
Hypercalcemia	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)
Normal	10 (14.1)	166 (43.0)	29 (18.8)	129 (39.1)
Hypocalcemia	40 (56.3)	177 (45.9)	88 (57.1)	98 (29.7)
Severe Hypocalcemia	2 (2.8)	5 (1.3)	3 (1.9)	2 (0.6)
Missing	19 (26.8)	36 (9.3)	34 (22.1)	101 (30.6)